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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,368	09/20/2001	Mieko Katsuura	447.001	8538

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,368	KATSUURA ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16 and 18* is/are allowed.

6)☒ Claim(s) *1-15,17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 04/29/2005 has been entered. Claims 1-19 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

Claims 1-15, 17, 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein that is a MP52 or BMP-2 antagonist, does not reasonably provide enablement for a protein that is a BMP-7 or BMP antagonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that MP52 shows the same general mechanism as other BMPs with respect to receptor binding and that the skilled artisan would expect a modified form of BMP-2 or -4 to be an effective antagonists against other BMPs. Applicant's arguments have been fully considered but they are not persuasive.

The term "antagonistic activity against BMPs" encompasses antagonistic activity against any and/or all BMPs. It is unclear exactly what the term "BMP antagonist-like activity" (claim 17) encompasses, but it is reasonable to construe this term as encompassing at least antagonistic activity against any and/or all BMPs. Accordingly, the claims are directed to or encompass:

> a modified MP52 having antagonistic activity against any and/or all BMPs or against MP52, BMP-2, BMP-4, or BMP-7; and,

a modified BMP-2, -4, or -7 having antagonistic activity against any and/or all BMPs.

However, members of the BMP family show different affinities to the different combinations of type I and type II receptors. See Yamashita (Bone. 1996 Dec;19(6):569-74) page 571, right column, full paragraph 2. Furthermore, Yamashita does not indicate that any and/or all BMPs are ligands for BMP type I receptors (BMPR-IA, BMPR-IB, ActR-I) and BMP type II receptors (ActR-II, ActR-IIB, and BMPR-II). See page 571, Table 1. In addition, at the time of Applicants' invention the contribution and identity of individual amino acid residues in BMPs to type I and type II receptor binding were unknown. It was also unknown at the time of Applicants' invention whether the same residues in given BMP that are responsible for binding to a particular type I and type II receptor are also responsible for binding to another type I or type II receptor, respectively. The fact that members of the BMP family show different affinities to the different combinations of type I and type II receptors provides a reasonable basis for the skilled artisan to question whether those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, whether a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and type II receptors, whether a particular, modified BMP would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors, and whether a particular, modified BMP would even be capable of adopting a conformation suitable for binding to any type I or type II BMP receptor.

Applicants have provided evidence that the modified MP52 of the present invention antagonizes the activity of MP52 in one system (MC3T3-E1 cells, Figure 2B) and antagonizes the activity of in BMP-2 another system (C3H10T½ cells, Figure 2A). Applicants have not provided any evidence that those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, whether a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and type II receptors, whether a particular, modified BMP would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors, and whether a particular, modified BMP would even be capable of adopting a conformation suitable for binding to any type I or type II BMP receptor. In view of the fact that members of the BMP family show different affinities to the different combinations of type I and type II receptors and the fact that at the time of Applicants' invention the contribution and identity of individual amino acid residues in BMPs to type I and type II receptor binding were unknown, the evidence provided by Applicants does not provide a reasonable basis for inferring that the modified proteins of the present invention would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors in any and/or all types of systems. In light of the state of the art at the time of Applicants' invention and Applicants' failure to provide any data demonstrating that those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, that a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and

type II receptors, that a particular, modified BMP would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors, and that a particular, modified BMP would even be capable of adopting a conformation suitable for binding to any type I or type II BMP receptor, the examiner concludes that Applicants have not enabled the full scope of the claimed invention.

Claims 1-15, 17, 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' argue that the modified MP52s and modified BMPs would have the same antagonistic activity against other BMPs since they all use the same general mechanism. Applicant's arguments have been fully considered but they are not persuasive.

The term "antagonistic activity against BMPs" encompasses antagonistic activity against any and/or all BMPs. It is unclear exactly what the term "BMP antagonist-like activity" (claim 17) encompasses, but it is reasonable to construe this term as encompassing at least antagonistic activity against any and/or all BMPs. Accordingly, the claims are directed to or encompass:

> a modified MP52 having antagonistic activity against any and/or all BMPs or against MP52, BMP-2, BMP-4, or BMP-7; and,
>
> a modified BMP-2, -4, or -7 having antagonistic activity against any and/or all BMPs.

However, members of the BMP family show different affinities to the different combinations of type I and type II receptors. See Yamashita (Bone. 1996 Dec;19(6):569-74) page 571, right column, full paragraph 2. Furthermore, Yamashita does not indicate that any and/or all BMPs are ligands for BMP type I receptors (BMPR-IA, BMPR-IB, ActR-I) and BMP type II receptors (ActR-II, ActR-IIB, and BMPR-II). See page 571, Table 1. In addition, at the time of Applicants' invention the contribution and identity of individual amino acid residues in BMPs to type I and type II receptor binding were unknown. It was also unknown at the time of Applicants' invention whether the same residues in given BMP that are responsible for binding to a particular type I and type II receptor are also responsible for binding to another type I or type II receptor, respectively. The fact that members of the BMP family show different affinities to the different combinations of type I and type II receptors provides a reasonable basis for the skilled artisan to question whether those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, whether a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and type II receptors, whether a particular, modified BMP would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors, and whether a particular, modified BMP would even be capable of adopting a conformation suitable for binding to any type I or type II BMP receptor.

Applicants have provided evidence that the modified MP52 of the present invention antagonizes the activity of MP52 in one system (MC3T3-E1 cells, Figure 2B) and antagonizes the activity of in BMP-2 another system (C3H10T½ cells, Figure 2A). Applicants have not

provided any evidence that those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, whether a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and type II receptors, whether a particular, modified BMP would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors, and whether a particular, modified BMP would even be capable of adopting a conformation suitable for binding to any type I or type II BMP receptor. In view of the fact that members of the BMP family show different affinities to the different combinations of type I and type II receptors and the fact that at the time of Applicants' invention the contribution and identity of individual amino acid residues in BMPs to type I and type II receptor binding were unknown, the evidence provided by Applicants does not provide a reasonable basis for inferring that the modified proteins of the present invention would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors in any and/or all types of systems. In light of the state of the art at the time of Applicants' invention and Applicants' failure to provide any data demonstrating that those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, that a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and type II receptors, that a particular, modified BMP would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors, and that a particular, modified BMP would even be capable of adopting a conformation suitable for binding

to any type I or type II BMP receptor, the examiner concludes that Applicants have not described the claimed invention.

Claims 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of antagonizing the activity of MP52 or BMP-2, does not reasonably provide enablement for therapy and/or prevention of symptoms of ectopic ossification which is related to BMPs, therapy and/or prevention of symptoms of metabolic diseases with calcification wherein said disease is related to the expression of BMPs, treating ectopic ossification which is related to BMPs, or treating metabolic diseases with calcification wherein said diseases are related to the expression of BMPs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that the claims have amended to more clearly indicate that the conditions are related to BMPs. Applicant's arguments have been fully considered but they are not persuasive.

The present specification indicates that "the causes of these diseases are still unknown in detail" (page 2, lines 22-23). There is no evidence of record that any BMP causes such diseases or symptoms or that an antagonist of any BMP would treat or prevent such diseases of the symptoms thereof. Furthermore, the claims are directed to or encompass the treatment of such diseases related to any and/or all BMPs. However, members of the BMP family show different affinities to the different combinations of type I and type II receptors. See Yamashita (Bone. 1996 Dec;19(6):569-74) page 571, right column, full paragraph 2. Furthermore, Yamashita does

not indicate that any and/or all BMPs are ligands for BMP type I receptors (BMPR-IA, BMPR-IB, ActR-I) and BMP type II receptors (ActR-II, ActR-IIB, and BMPR-II). See page 571, Table 1. In addition, at the time of Applicants' invention the contribution and identity of individual amino acid residues in BMPs to type I and type II receptor binding were unknown. It was also unknown at the time of Applicants' invention whether the same residues in given BMP that are responsible for binding to a particular type I and type II receptor are also responsible for binding to another type I or type II receptor, respectively. The fact that members of the BMP family show different affinities to the different combinations of type I and type II receptors provides a reasonable basis for the skilled artisan to question whether those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, and whether a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and type II receptors.

Applicants have provided evidence that the modified MP52 of the present invention antagonizes the activity of MP52 in one system (MC3T3-E1 cells, Figure 2B) and antagonizes the activity of in BMP-2 another system (C3H10T½ cells, Figure 2A). Applicants have not provided any evidence that those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, and whether a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and type II receptors. In view of the fact that members of the BMP family show different affinities to the different combinations of type I and type II receptors and the fact that at the time of Applicants'

invention the contribution and identity of individual amino acid residues in BMPs to type I and type II receptor binding were unknown, the evidence provided by Applicants does not provide a reasonable basis for inferring that the modified proteins of the present invention would antagonize the binding of any and/or all BMPs or MP52 to any and/or all combinations of BMP type I and type II receptors in any of the disease states for which treatment or prevention is desired. In light of the state of the art at the time of Applicants' invention and Applicants' failure to provide any data demonstrating that those residues in MP52 that are involved in binding to one particular combination of type I and type II receptors are also involved in binding of MP52 to another combination of type I and type II receptors, that a modified MP52 would antagonize the binding of any and/or all BMPs to any and/or all combinations of BMP type I and type II receptors, the examiner concludes that Applicants have not enabled the full scope of the claimed invention.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The term "related" in claims 12-15 is a relative term which renders the claim indefinite. The term "related" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. The "relatedness" of the BMPs or expression of the BMPs to the disease is unclear. The metes and bounds are not clearly set forth. It is

suggested that the claims be limited to diseases due to the ectopic expression of BMPs, as supported by page 2, lines 25-28, of the specification.

Conclusion

Claims 16 and 18 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JULY 21, 2005